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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/056,347	BURCH ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,47,48 and 53-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,47,48 and 53-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/9/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 3/14/08 and 11/5/02 have been entered. Claims 38 and 47-52 were pending. Applicants amended claim 38 and canceled claims 49-52. In addition, claims 53-62 were added. Thus, claims 38, 47, 48, and 53-62 are currently pending. Applicants' election of species is noted (e.g., see 3/14/08 response). Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)). Thus, claims 38, 47, 48, 53-62 are examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All rejections are withdrawn in view of Applicants' arguments and/or amendments in favor of the newly cited rejections below.

New Rejections

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 54 and 57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain associated with COX-1/2 receptors and/or opioid receptors, does not reasonably provide enablement for every type of pain associated with the laundry list of possibilities cited in claim 54 caused by any underlying receptor/agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: Claim 54, for example, is drawn to a method for treating various types of pain including cancer pain, post-surgical pain, low back and neck pain … etc. However, the nature of the invention cannot be fully determined because the invention has not been defined with particularity. For example, the claims would encompass "pain" that has nothing to do with receptors that meloxicam/oxycodone are known to react with. For example, opioid analgesic medication like oxycodone are known to react with opioid receptors (e.g., see Wikipedia, the Free Encyclopedia. Oxycodone. Retrieved at on May 26, 2008 from http://en.wikipedia.org/wiki/Oxycodone, pages 1-10, especially page 1, paragraph 1; see also Wikipedia, the Free Encyclopedia. Opioid. Retrieved at on May 26, 2008 from http://en.wikipedia.org/wiki/opioid, pages 1-10, especially page 1, paragraph 1) whereas Meloxicam is known to selectively inhibit COX-2 over COX-1 (e.g., see Wikipedia, the Free Encyclopedia. Meloxicam. Retrieved at on May 26, 2008 from http://en.wikipedia.org/wiki/Meloxicam, pages 1-3, especially pages 1). However, terms like "cancer pain", "post-surgical" pain, etc. would include all pain associated with cancer, post-surgical trauma, etc. that would read well beyond the pain pathways associated with opioid/COX receptors noted above. For example, cancer pain, pain associated post-surgical amputation, pain associated with multiple sclerosis, etc. can be associated with many different receptors/pathways such as TRPV1 (e.g., see Wikipedia, the Free Encyclopedia. TRPV1. Retrieved at on May 26, 2008 from

http://en.wikipedia.org/wiki/TRPV1, pages 1-7, especially pages 2 and 3) and there is no evidence, nor do Applicants suggest such in their application, that oxycodone/meloxicam would have any effect whatsoever on such receptors. In addition, pain may be relieved by "curing" the underlying causative agent. That is, if cancer could be prevented or cured then the pain that was associated with this cancer would necessarily be alleviated as well. Thus, the claimed scope also reads on treating/curing the underlying cause of the pain, not just the receptors associated with the pain mechanism of action.

(3 and 5) The state of the prior art and the level of predictability in the art: The prior art indicates that no one combination of drugs can treat every pain related ailment or pathway. For example, the article by Andrew Pollack (Pollack, A. "The Search for the Killer Painkiller" downloaded from http://opioids.com/pain/painkillers.html on May 26, 2008, pages 1-12) discuses many different pathways associated with pain and further notes various limitations for several medical tactics for treating such pain. For example, Pollack states, "Nsaids don't work for neuropathic pain [i.e., Meloxicam], specialist say, and there is disagreement on how effective opioids [i.e., oxycodone] are" (e.g., see page 5). In addition, Pollack states, "there is also a need for totally new categories of pain relievers, ones that work in entirely different ways … A different approach [than Nsaids/opioids] would be to block the sensors on nerve cells activated by capsaicin, called the TRPV1" (e.g., see pages 6 & 8). Finally, Pollack notes that a drug therapy must be tailored to the mechanisms underlying that person's pain (e.g., see page 1). So if, the mechanism involves irregular TRPV1 modulation than a person of skill in the art

would no expect Nsaids and/or opioids, which effectuate pain relieve by a completely different mechanism, to have any effect whatsoever. Further, the article by Jonathan Cole states that pain like "phantom limb pain" associated with post-surgical procedures like amputation are almost "impossible" to treat (e.g., see Cole, S. "Phantom limb pain" downloaded from http://www.wellcome.ac.uk/en/pain/microsite/medicine2.html on May 26, 2008, pages 1-4, especially page 1, paragraph 1, "Phantom limb pain – pain appearing to come from where an amputated limb used to be – is often excruciating and almost impossible to treat"; see also last paragraph, "Unfortunately, phantom limb pain is generable intractable and chronic; once it develops it persists and is rarely improved by present medical treatments"). Likewise, the article by the National Institutes of Health U.S. Department of Health and Human Services echo how difficult it can be to treat pain, especially chronic pain, and the mechanism of action are not well understood (e.g., see National Institutes of Health U.S. Department of Health and Human Services, "An update of NIH Pain Research and Related Program Initiatives, testimony delivered on December 8, 2005 before Subcommitte on Health Committee on Energy and Commerce United States House of Representatives, pages 1-21, especially, page 9, "Sizeable gaps exist in our understanding of some of the most basic cellular interactions involved in the pain process … The NIH recently launched an effort to stimulate needed research into the basic biology of … pain disorders … [as a result] key aspects of the pain process will be more clearly defined, pointing the way to unique and highly specific molecular targets for drug development. Without identifying these additional targets, it will be impossible to

ever adequately control or treat pain, particularly among Americans who suffer from chronic pain"). Further, the prior art recognized that there is no known cure for many of the causative agents recited in Applicants' Markush list and, as a result, pain could not be alleviated by curing the underlying condition either (e.g., see Rittenberg, C. N., "Positive thinking: an unfair burden for cancer patients? *Support Care Cancer* **1995**, *3*, 37-39, especially page 38, column 1, first full paragraph).

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have not provided examples commensurate in scope with the current claims. For example, Applicants have not provided examples how to treat pain associated with receptors like TRPV1. Applicants have only provided examples on how to treat pain on a select group of patients with osteoarthritis (e.g., see Examples 1 and 2).

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). In this case, Applicants have not provided any working

examples that would teach this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation. Please note that this is a "scope of enablement" rejection.

Claim Rejections - 35 USC § 103

4. Claims 38, 47, 48, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. (U.S. Patent No. 4,569,937) (Date of Patent is **Feb 11, 1986**) (of record) in view of Furst (Furst, D. E. "Meloxicam: Selective COX-2 inhibition in clinical practice" *Seminars in Arthritis and Rheumatism*, **June 1997**, *26(1)*, 21-27) (of record) and in further view of Oshlack I et al. US Pat. No. 5,472,712 **(December, 1995)** (of record) and/or Oshlack II et al. US Pat. No. 6,294,195 (9/01: effectively filed **October, 1993** or earlier) (of record) and Iyengar et al. (WO 97/25988) (Date of Patent is **July 24, 1997**) (of record) and as evidenced by Wikipedia if necessary (Wikipedia, the Free Encyclopedia. Meloxicam. Retrieved at on May 26, 2008 from http://en.wikipedia.org/wiki/Meloxicam, pages 1-3).

For ***claim 38***, Baker et al. (see entire document) teach a method of effectively treating pain in humans comprising orally administering to a human patient an oral dosage form comprising two analgesic compounds and or pharmaceutically acceptable salts thereof (e.g., see abstract, "Pharmaceutical compositions of narcotic analgesics [i.e., compound #1] and ibuprofen [i.e., compound #2] have been found to exhibit

unexpectedly enhanced analgesic activity [i.e., pain relief] … This synergism enables the use of lower doses of either or both drugs [i.e., two analgesic compounds] with a concomitant reduction in risk of possible side effects"; see also column 3, paragraph 1 wherein administration to a "human" is disclosed; see also column 2, lines 44-48 wherein an "oral" dosage is disclosed, "Oxycodone … are preferred because of their strong potency in oral dosage forms. Oxycodone is most preferred"; see also Examples, especially Example 1 wherein use pharmaceutical dosage forms containing "only" oxycodone and ibuprofen are set forth; see also columns 3-8 wherein "single dosage form" is disclosed; see also columns 8 and 9 wherein sequential administration is disclosed; see also columns 3 and 4 showing "sustained release" formulations). In addition, Baker et al. disclose the use of oxycodone and/or at least one pharmaceutically acceptable salt in the composition (e.g., see column 2, lines 44-48 wherein an "oral" dosage is disclosed, "Oxycodone … are preferred because of their strong potency in oral dosage forms. Oxycodone is most preferred"; see also columns 1, 2, 8-10; see also Examples, especially Example 1 wherein the use of pharmaceutical dosage forms containing "only" oxycodone and ibuprofen are set forth). In addition, Baker et al. teach the use of oxycodone and/or at least one pharmaceutically acceptable salt thereof in an amount from 2.5 mg to 800 mg in an oral dosage form (e.g., see Example 1 wherein 5 mg is disclosed; see also Examples 2-24; see also column 2; see also column 3, dosage forms section). Baker et al. also disclose the use of an NSAID like meloxicam in an amount from bout 0.5 mg to about 1500 mg for the oral dosage form (e.g., see Example 1

wherein 60 mg of Ibuprofen NSAID is disclosed; see also Examples 2-24; see also columns 2 and 3).

For ***claim 47***, Baker et al. disclose a ratio of oxycodone and/or at least one pharmaceutically acceptable salt thereof to NSAID and/or at least one pharmaceutically acceptable salt thereof is from about 0 0001:1 to about 1:1 (e.g., see column 2, lines 14-19, "(a) a narcotic analgesic [i.e., oxycodone], or a pharmaceutically acceptable salt thereof, and (b) ibuprofen [i.e., substituted by Meloxicam, see below], or a pharmaceutically suitable salt thereof, in which the weight ratio of (a):(b) is from about 1:1 to about 1:800. Preferred ratios of (a):(b) are from about 1:3 to about 1:400, and most preferred ratios are from about 1:30 to about 1:400"; see also claim 1).

For ***claim 48***, Baker et al. teach oxycodone is present in the pharmaceutically acceptable salt form (e.g., see claim 1, "A pharmaceutical composition comprising a synergistic analgesic combination of (a) oxycodone, or pharmaceutically acceptable salt thereof").

The prior art teachings of Baker et al. differ from the claimed invention as follows:

For ***claim 38, 47, 48***, Baker et al. fail to disclose compositions with Meloxicam. Baker et al. only teach the use of other NSAIDs like ibuprofen (e.g., see Baker et al., abstract). In addition, Baker et al. fail to teach the use of "a sustained release carrier in an amount such that said oral dosage form provides a therapeutic effect for about 12 hours or longer."

For ***claim 53***, Baker et al. fail to specify the types of sustained release carriers that can be used only noted that sustained release carriers can be used in general (e.g., see Baker, column 3, second to last full paragraph).

For ***claim 54***, Baker et al. fail to teach the Markush of listed pains like Cancer pain. Baker et al. only talks about alleviating pain in general (e.g., see claim 4 drawn to a method of alleviating pain).

However, the combined references of Furst, Oshlack I/II et al. and Iyengar et al. teach the following limitations that are deficient in Baker et al.:

For ***claim 38, 47, 48***, the combined references of Furst, Oshlack I/II et al. and Iyengar et al. teach the use of Meloxicam to alleviate pain in human patients (e.g., see Furst, figure 1; see also page 23, column 2, paragraph 1 "Nabumetone was significantly … more effective than placebo and had comparable efficacy to naproxen or aspirin in the physicians' and patients' assessment of degree of pain … [further studies] showed meloxicam [7.5 mg] to have efficacy approximately equal to that of nabumetone 1,000 mg"). Thus, Meloxicam is even more effective than other NSAIDs like Nabumetone at reducing pain and can be used in smaller dosages (i.e., 7.5 mg compare to 1,000 mg). Furthermore, Meloxicam exhibits less serious gastric and renal side effects than ibuprofen because it selectively inhibits COX-2 rather than COX-1 (e.g., see Furst, abstract, "inhibition of the COX-1 isoform produces the troublesome and sometimes serious gastric and renal side effects of NSAIDs. A relatively selective COX-2 inhibitor, such as meloxicam, may … [exhibit] improved tolerability"; see also page 22, column 1,

last paragraph, "Meloxicam exhibited greater COX-2 selectivity than … ibuprofen … [which] preferentially inhibited COX-1"; see also "Safety of Meloxicam" section starting on page 24, especially, column 2, paragraph 1, "Meloxicam 7.5 mg caused no significant change in the mucosal appearance … With piroxicam, there was a significantly higher number of endoscopically detected ulcers developing during the study compared with the meloxicam 15 mg group"; see also figure 2; see also page 24, column 2, paragraph 2, "During this large 4-week trial, GI side effects were significantly more common in the diclofenac group (19%) than in the meloxicam group (13%) … diclofenac caused significantly more dyspepsia, abdominal pain, nausea and vomiting, and diarrhea than meloxicam"; see also Table 2 showing meloxicam to be the "safest" NSAID especially with regard to gastrointestinal events; see also page 26, column 1, paragraph 1 showing meloxicam to be "well suited for the elderly" because the drug is "almost entirely converted to inactive metabolites before excretion"; see also Figure 3; see also Conclusions section, especially page 26, column 2, last paragraph, "Taken together, these results show that meloxicam has a good safety and efficacy profile, with some indication of increased GI safety over several other NSAIDs. The possible explanation for this profiles meloxicam's relatively selective inhibition of COX-2"; see also table 1 showing meloxicam has a better COX-2/COX-1 profiile than ibuprofen). Furst also disclose, for example, 7.5 and 15 mg doses for Meloxicam (e.g., see Table 2), which meets the from about 0.5 mg to about 1500 mg limitation for the amounts of drug present in the oral dosage form.

In addition, the combined references of Furst, Oshlack I/II et al. and Iyengar et al. teach the use of sustained release dosage forms for opioid analgesics, including oxycodone, which utilize sustained release carriers such as beads coated with the opioid drug or substrate layers enclosing the opioid drug for the purpose of effectuating this sustained release (e.g., see Oshlack I, abstract, "A stabilized solid controlled release formulation …"; see also column 14, paragraph 2, "A wide variety of therapeutically active agents can be used in conjunction with the present invention … [including] oxycodone"; see also column 13, line 34; see also claim 6; see also claim 50; see also claim 62; see also claim 86; see also claim 108; see also Oshlack II, abstract, see also claims; see also examples; see also column 6, line 48; see also claim 5).

The combined references of Furst, Oshlack I/II et al. and Iyengar et al. also teach the use of sustained release for Meloxicam (e.g., see Iyengar et al., paragraph bridging pages 46 and 47, "The present invention encompasses … Meloxicam"; see also page 47, first full paragraph, "The advantages of any synergistic combination therapy are obvious … Sustained release formulations are now more feasible due to the lower amounts of active ingredient necessary"; see also paragraph bridging pages 48 and 49, "The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art"). In addition, the combined references of Oshlack I/II et al. and Iyengar et al. also teach a therapeutic effect for about 12 hours or longer (e.g., see Oshclack II, abstract, "provide effective blood levels of the opioid analgesic for at least

about 24 hours"). In addition, Wikipedia states that Meloxicam is known to have a long half life (i.e., 15 to 20 hours) and thus would be expected to have a therapeutic effect for at least 15 to 20 hours even in the absence of a controlled release formulation. (e.g., see Wikipedia, the Free Encyclopedia. Meloxicam. Retrieved at on May 26, 2008 from http://en.wikipedia.org/wiki/Meloxicam, page 1).

For ***claim 53***, the combined references of Furst, Oshlack I/II et al. and Iyengar et al. teach the use of sustained release carriers such as Applicants' elected alkylcellulose (e.g., see Oshlack I, title; see also column 2, second full paragraph, "It considered very desirable in the art, however, to provide a controlled release coating derived from aqueous dispersions of a hydrophobic material, such as ethyl cellulose [i.e., and alkylcellulose]"; see also column 1, lines 56-58, "Hydrophobic polymers such as certain cellulose derivatives, zein, acrylic resins, waxes, higher aliphatic alcohols, and polylactic & polyglycolic acids have been used in the prior art to develop controlled release dosage forms.").

For ***claim 54***, the combined references of Furst, Oshlack I/II and Iyengar et al. teach application of analgesics to treat, for example, Applicants' elected cancer pain (e.g., see Iyengar et al., page 47, second to last paragraph, "Such pains include chronic pain, such as neuropathic pain, and post-operative pain, pain associated with arthritis, cancer-associated pain, chronic lower back pain, cluster headaches, herpes neuralgia, phantom limb pain, central pain, dental pain, neuropathic pain, opioid-resistant pain, visceral pain, surgical pain, bone injury pain, pain during labor and delivery, pain resulting from burns,

including sunburn, post partum pain, migraine, angina pain, and genitourinary tract-related pain including cystitis."; see also Oshlack II, column 1, line 54).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute Meloxicam as taught by the combined references of Furst, Oshlack I/II et al. and Iyengar et al. for the ibuprofen in the ibuprofen/oxycodone compositions as taught by Baker et al. because, for example, Furst shows that meloxicam is more potent than any other NSAID at reducing pain in clinical trials (e.g., see figure 2). Furthermore, a person of skill in the art would have been motivated to use Meloxicam not only because it is more potent but also because it is safer than other NSAIDs including the ibuprofen disclosed by Baker et al. (e.g., see Furst, abstract, "inhibition of the COX-1 isoform produces the troublesome and sometimes serious gastric and renal side effects of NSAIDs. A relatively selective COX-2 inhibitor, such as meloxicam, may … [exhibit] improved tolerability"; see also page 22, column 1, last paragraph, "Meloxicam exhibited greater COX-2 selectivity than … ibuprofen … [which] preferentially inhibited COX-1"; see also "Safety of Meloxicam" section starting on page 24, especially, column 2, paragraph 1, "Meloxicam 7.5 mg caused no significant change in the mucosal appearance … With piroxicam, there was a significantly higher number of endoscopically detected ulcers developing during the study compared with the meloxicam 15 mg group"; see also figure 2; see also page 24, column 2, paragraph 2, "During this large 4-week trial, GI side effects were significantly more common in the diclofenac group (19%) than in the meloxicam group (13%) … diclofenac caused

significantly more dyspepsia, abdominal pain, nausea and vomiting, and diarrhea than meloxicam"; see also Table 2 showing meloxicam to be the "safest" NSAID especially with regard to gastrointestinal events; see also page 26, column 1, paragraph 1 showing meloxicam to be "well suited for the elderly" because the drug is "almost entirely converted to inactive metabolites before excretion"; see also Figure 3; see also Conclusions section, especially page 26, column 2, last paragraph, "Taken together, these results show that meloxicam has a good safety and efficacy profile, with some indication of increased GI safety over several other NSAIDs. The possible explanation for this profiles meloxicam's relatively selective inhibition of COX-2"). Finally, a person of skill in the art would reasonably have expected to be successful because Meloxicam has been shown through extensive human clinical trials to be safe and effective especially with regard to the gastrointestinal tract (see Furst citations above), which is a preferred route of administration disclosed by Baker et al. (e.g., see Baker et al., column 4, line 13). In addition, Baker et al. explicitly state in the Background section that NSAIDs have been used to treat pain (e.g., see Baker et al., column 1, paragraph 3, "This patent discloses that the analgesic effect of the combination of a selected NSAID and a selected narcotic analgesic is greater than for either alone"), which would include Meloxicam (e.g., see abstract, "Nonsteroidal antiinflammatory drugs (NSAIDs) exert their actions by inhibiting cyclooxygenase (COX) … A relatively selective COX-2 inhibitor … [is] meloxicam [i.e., Meloxicam is an NSAID]"). Furthermore, Furst explicitly state that meloxicam is safer than ibuprofen (e.g., see Furst, page 22, column 1, last paragraph).

Alternatively, it is submitted that the mere substitution of one component for another to yield predictable results represents a *prima facie* case of obviousness. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 2007 WL 1237837, at *12 (2007). Here, it would be obvious to make a simple substitution of Meloxicam for ibuprofen because it was known at the time of filing that both provided the same antiinflammatory relief via inhibition of COX receptors (e.g., see Furst, abstract; see also Table 1). Furthermore, this substitution would have led to predictable results based on the combined teachings noted above because again it was well known that both drugs inhibit the same COX 1/2 receptors to produce the same/similar results. Thus, a person of ordinary skill in the art would have expected antiinflammatory efficacy whether ibuprofen or meloxicam was used.

In addition, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to utilize sustained release carriers for oxycodone including beads/layers as taught by the combined references of Furst, Oshlack I/II et al. and Iyengar et al. for use in the Baker compositions since Baker expressly states that sustained release formulations are desirable. Furthermore, a person of ordinary skill in the art would have been motivated to use these formulations to delay drug release for extended duration (e.g., see Oshclack II, abstract, ""provide effective blood levels of the opioid analgesic for at least about 24 hours"). In addition, a person of skill in the art would have been motivated to use oxycodone in a sustained release dosage because, according to Oschlack I, "The present invention provides many benefits over prior art

coatings, including, but not limited to, avoidance of organic solvents which have inherent safety concerns (flammability, carcinogenicity, environmental concerns, safety in general), and extended stability which may result in extended shelf life and expiration dating" (e.g., see Oschlack I, column 5, paragraph 3). Furthermore, Oshclack II state, "provide effective blood levels of the opioid analgesic for at least about 24 hours" using controlled release (e.g., see abstract). Finally, a person of skill in the art would have reasonably expected to be successful because the combined references of Oshlack I/II et al. and Iyengar teach that these formulations can be used for opioid analgesics like Applicants' preferred oxycodone or NSAIDs like Applicants' preferred Meloxicam (e.g., see Oshlack I, claims 6, 50, 62, 86 and 108; see also Iyengar et al., paragraph bridging pages 46 and 47, "The present invention encompasses ... Meloxicam"; see also page 47, first full paragraph, "The advantages of any synergistic combination therapy are obvious ... Sustained release formulations are now more feasible due to the lower amounts of active ingredient necessary"; see also paragraph bridging pages 48 and 49, "The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art").

5. Claims 38, 47, 48, 53-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. (U.S. Patent No. 4,569,937) (Date of Patent is **Feb 11, 1986**) (of record) and Furst (Furst, D. E. "Meloxicam: Selective COX-2 inhibition in clinical practice" *Seminars in Arthritis*

and Rheumatism, **June 1997**, *26(1)*, 21-27) (of record) and Oshlack I et al. US Pat. No. 5,472,712 **(December, 1995)** (of record) and/or Oshlack II et al. US Pat. No. 6,294,195 (9/01: effectively filed **October, 1993** or earlier) (of record) and Iyengar et al. (WO 97/25988) (Date of Patent is **July 24, 1997**) (of record) in further view of Eichel et al. (U.S. Patent No. 5,376,384) **(December 27, 1994)** and Miller et al. (EP 0649657 A1) (Date of patent is **April 26, 1995)** as evidenced by Wikipedia if necessary (Wikipedia, the Free Encyclopedia. Meloxicam. Retrieved at on May 26, 2008 from http://en.wikipedia.org/wiki/Meloxicam, pages 1-3).

For ***claims 38, 47, 48, 53 and 54***, the combined references of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al. teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 38, 47, 48, 53 and 54. *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) ("anticipation is the epitome of obviousness"); see also *In re Skoner*, 517 F.2d 947, 950, 186 USPQ 80, 83 (CCPA 1975); *In re Pearson*, 494 F.2d 1399, 1402, 181 USPQ 641, 644 (CCPA 1974).

For ***claims 55-57, 61 and 62***, the combined references of Baker et al., Furst, Oshalck I et al., Oshlack II et al., and Iyengar et al., teach all the limitations noted above in the first Baker et al. rejection (which are incorporated in their entireties herein by reference). For example, the limitations for claim 55 can be found in part in the discussion of claim 38 mentioned above. Likewise, the limitation for claim 56 can be found in the discussion of claim 53. Similarly, the limitations noted in claim 57 can be found in the discussion of claim 54 noted above.

For ***claims 58 and 59***, the combined references also teach the method of claim 55 wherein said dosage from comprises particles, wherein said particles have diameter from about 0.1 mm to about 2.5 mm (e.g., see Oshlack I, column 9, lines 31-39, "In one preferred embodiment of the present invention, the controlled release dosage form comprises pharmaceutically acceptable beads (e.g., spheroids) [i.e., particles] containing - the active ingredient coated with a controlled release coating. The term spheroid is known in the pharmaceutical art and means, e.g., (a spherical granule having a diameter of between 0.2 and 2.5 mm especially between 0.5 and 2.0 mm").

The prior art teaching of the combined references of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al. differ from the claimed invention as follows:

For ***claims 55-62***, the combined references of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al. fail to teach the use of an immediate-release formed used in conjunction with a sustained release form. More specifically the combined references fail to teach an immediate release form for meloxicam and a sustained release form for oxycodone.

For ***claims 60***, the combined references of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al.fail to teach the method of claim 55 wherein the meloxicam is coated onto a table comprising oxycodone in sustained release form.

However, the combined references of Eichel et al. and Miller et al. teach the following limitations that are deficient in the combined references of Baker et al., Furst,

Oshlack I et al., Oshlack II et al., and Iyengar et al.:

For ***claim 55-62***, the combined references of Eichel et al. and Miller et al. (see entire documents) teach the virtues of using both an immediate and sustained release dosage form (e.g., see Eichel et al., column 3, lines 10-24, "in some instances, it is desirable to mix the delayed sustained-release preparation with an immediate release drug to obtain a biphasic drug release profile … The sustained-release formulation may be part of a multi-layered table containing an immediate-release layer of acetaminophen to quickly elevate and then maintain the blood levels of acetaminophen"; see also lines 25-39; see also column 5, lines 7-11, "The multi-unit microparticles may also be admixed or concentrically coated with other fractions of an immediate-release drug to provide for both immediate and delayed sustained release of the drug"; see also lines 12-18; see also column 6, lines 37-48; see also Miller et al., paragraph bridging pages 2 and 3, ""Medicaments produced using the NSAID [i.e., meloxicam] and opioid analgesic [i.e., oxycodone] … may take a wide variety of forms … [including formulations that] give immediate release of the active ingredients upon administration or may be adapted to give delayed or sustained release or … a combination of both immediate and delayed or sustained release"). Note also that said dosage forms are effective via 12 or 24 hours (e.g., see Miller et al., claim 3). Note also the amounts for the NSAID/opioid analgesic used in the reference (e.g., see claim 8) and the disease associated pains that are being treated such as arthritis (e.g., see abstract).

For ***claims 60 and 61***, the combined references if Eichel et al. and Miller et al.

teach the use of coating the immediate release form on the surface of a table containing the sustained release form and additionally disclose, in addition to the teachings of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al. noted above, wherein said sustained release carrier being (i) a sustained release coating; or (ii) incorporated into a matrix with said oxycodone (e.g.., see Eichel et al., column 3, lines 20-24, "The sustained-release formulation may be part of a multi-layered tablet containing an immediate-release layer … to quickly elevate and then maintain the blood levels [of the drug]"; see also column 4, last paragraph, The core drug may be coated on sugar spheres, blended with wax incipient, or otherwise formulated to produce core drug granules. Preferably, the core drug granules are spherical microparticles having a size range from about 500 to 15 microns"; see also column 5, paragraphs 2 and 3; see also column 6, last three paragraphs; see also claim 17, The pharmaceutical preparation of claim1 6 wherein said delayed, sustained-release component is in the form of multi-units of microparticles").

For ***claim 62***, the combined references of Eichel et al., and Miller et al. also disclose, in addition to the teachings of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al. noted above, the requisite 24 hour release (e.g., see Eichel et al., column 1, lines 47 and 48, "sustained release over periods of 4 to 24 hours").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a biphasic (sustained + immediate release) drug as taught by Eichel et al. using the oxycodone + meloxicam combination as taught by the

combined references of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al. because obtaining the best drug release profile is a goal for the administration of any drug. Furthermore, a person of ordinary skill in the art would have been motivated to use the biphasic sustained + immediate release dosage to provide both a "quick elevation" and a longer term "maintenance" of the drug in the blood (e.g., see Eichel et al., column 3, lines 10-24, "in some instances, it is desirable to mix the delayed sustained-release preparation with an immediate release drug to obtain a biphasic drug release profile … The sustained-release formulation may be part of a multi-layered table containing an immediate-release layer of acetaminophen to quickly elevate and then maintain the blood levels of acetaminophen"). Furthermore, a person of ordinary skill in the art would reasonably have expected to be successful because Oshlack I, for example, teaches that oxycodone can easily be formulated into a sustained release table (e.g., see Oshlack I, abstract, "A stabilized solid controlled release formulation …"; see also column 14, paragraph 2, "A wide variety of therapeutically active agents can be used in conjunction with the present invention … [including] oxycodone"). In addition, Miller et al. state, "Medicaments produced using the NSAID [i.e., meloxicam] and opioid analgesic [i.e., oxycodone] … may take a wide variety of forms … [including formulations that] give immediate release of the active ingredients upon administration or may be adapted to give delayed or sustained release or … a combination of both immediate and delayed or sustained release" (e.g., see paragraph bridging pages 2 and 3) (emphasis added).

Response

6. To the extent that Applicants' arguments could be applied against the newly cited rejections above, the following comments are noted:

[1] Applicants argue that the cited references do not teach the "12 hours or longer" dosage forms (e.g., see 11/5/07 Response, page 6).

[1] It is respectfully submitted that this limitation is taught as outlined in the newly amended rejections above.

[2] Applicants' argue, "although ibuprofen and meloxicam may both act on COX-1 and COX-2 receptors, the specificity of ibuprofen and meloxicam for these receptors I different and these receptors are located in different parts of the body … [consequently a person of skill in the art] would not know what the exact result would be if ibuprofen was substituted with meloxicam" (e.g., see paragraph bridging pages 6 and 7).

[2] Obviousness does not require absolute predictability of success; rather, all that is required for obviousness under § 103 is a "reasonable expectation of success." In re O'Farrell, 853 F.2d at 903-904 [7 USPQ2d at 1681]. Here, a person of skill in the art would readily appreciate that selective COX-2 inhibitors are more desirable than non-selective COX-2 inhibitors. Furthermore, as of the filing date, many such drugs were studied with different profiles including diclofenac, piroxicam, naproxen, etc., which painted a very good picture of the landscape with regard to the results that could be obtained by varying such selectivity.

[3] Applicants argue, "the Examiner [should] reconsider the arguments presents in the

response filed on May 30, 2007" (e.g., see page 6).

[3] The Examiner has reconsidered the arguments as requested but finds that the claims are properly rejected for the reasons of record and those noted in this office action.

[4] Applicants argue, "With regard to new claim 55 ... the cited references does not teach or suggest ... immediate release form" (e.g., see bottom of page 7; see also bottom of page 8 wherein this same argument is set forth again).

[4] The Examiner agrees and has added a new 35 U.S.C. § 103(a) rejection to address these newly added limitations.

[5] Applicants argue that the cited references do not provide a "direct comparison" of the effects of iburopfen and meloxicam in the body (e.g., see middle page 8).

[5] It is respectfully submitted that this issue was adequately addressed in the 11/5/07 Response (see page 12, answer 5).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jon D. Epperson/
Primary Examiner, AU 1639